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# Immunodeficiency as a Component of Recognizable Syndromes

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**Immunodeficiency occurs in numerous genetic syndromes. While it is the dominant manifestation in primary immunodeficiencies, immune deficits may also be seen in a variety of other recognizable syndromes. Immunodeficiency has been reported in 64 such conditions, adding to the 45 recognized primary immunodeficiencies. These uncommon syndromes with immune defects can present with: (a) growth deficiency (11 syndromes with disproportionate or proportionate short stature), (b) specific organ system dysfunction (18 with gastrointestinal, dermatologic, or neurologic abnormalities), (c) inborn errors of metabolism (13), (d) miscellaneous anomalies (10), or (e) chromosome anomalies (12). In most of the disorders, only some of the affected patients have immune defects. However, in 27 syndromes, immunodeficiency is a constant finding. We briefly review the clinical manifestations of each syndrome and delineate the specific associated immune defects. In most syndromes, the connection between the immune and other defects is unknown. Recognition of these conditions involving both the immune and other organ systems may facilitate accurate diagnosis and management as well as yield information regarding genes critical for the development of the involved systems.**


**KEY WORDS: immunodeficiency syndromes, growth disorders, T cells, cellular immunity, B cells, humoral immunity**

**Abbreviations**

| | |
|---|---|
| ADA | adenosine deaminase |
| ConA | concanavalin A |
| DTH | delayed type hypersensitivity |
| Ig | immunoglobulin |
| MLC | mixed leukocyte culture |
| NBT | nitroblue tetrazolium |
| NK | natural killer cell |
| PHA | phytohemagglutinin |
| PNP | purine nucleoside phosphorylase |
| PWM | pokeweed mitogen |

## INTRODUCTION

Many children with syndromes have an increased susceptibility to infection. Although the increased rate of infection is sometimes associated with poor control of swallowing and resultant aspiration, structural abnormalities, chronic disease, or malnutrition, in some cases no such cause can be identified. In many of these conditions, study of the immune system has been helpful. A number of immune defects have been identified, sometimes in single case reports, and in others, as a constant manifestation in the syndrome.

Immune defects can involve any of the limbs of the immune system: the humoral (B cell), cellular (T cell), phagocytic (neutrophils or monocytes), natural killer cell, or complement system. Severe defects lead to symptoms such as chronic or recurrent infection, infection with unusual agents, or poor response to treatment. Laboratory examination for immunodeficiency should be performed on individuals presenting with these complaints. Clinically significant immunodeficiency will present with both an unusual history of infection and confirmatory laboratory tests.

Many of the immunodeficiency syndromes have a genetic basis, and most of these conditions present with clinical signs and symptoms related solely to the immunological defect. The World Health Organization has classified the primary immunodeficiencies [Rosen et al., 1995]. Some immunodeficiency syndromes present with other manifestations. Immune defects may occur in the setting of diverse other characteristics, such as metabolic derangements, faulty embryogene-

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sis, chromosome abnormalities, or other organ system involvement. This paper will delineate those immunodeficiencies which are recognizable genetic syndromes.

## SYNDROMES ASSOCIATED WITH GROWTH DEFICIENCY

Several immunodeficiency syndromes are associated with growth deficiency (Table I). These may be further categorized by the characteristics of the short stature. Disproportionate short stature occurs when the limbs are short compared to the trunk, when the trunk is short in relation to the limbs, or some combination of both types of shortness. Such disproportionate short stature is usually considered to be a form of "dwarfism," or the consequence of a skeletal dysplasia. Short stature may also be proportionate, in which case the overall height is small, but the various body parts are commensurate with one another.

### Disproportionate Short Stature

The disproportionate short stature that occurs with immunodeficiency usually affects the limbs more than trunk, resulting in short-limb skeletal dysplasia (SLSD). Ammann et al. [1974] propose three categories of immune deficiency associated with this type of short stature. Type 1 consists of short-limb skeletal dysplasia in association with combined immunodeficiency; Type 2 is associated with a predominantly cellular immune defect, and Type 3 presents primarily with a humoral immune defect. Most of these disorders appear to be inherited as autosomal recessive traits.

***Short-limb skeletal dysplasia with severe combined immunodeficiency.*** These patients appear to be a heterogeneous group. Some have adenosine deaminase (ADA) deficiency [MacDermot et al., 1991], but some cases with prenatal onset severe short-limb skeletal dysplasia have not been tested for ADA deficiency. Generally, individuals with ADA deficiency have relatively mild metaphyseal abnormalities, often affecting the ribs. Other patients have more severe shortening of the limbs. In these patients, ADA levels have not been determined. One such patient presented with proximal shortness of the lower limbs and increased skin folds [MacDermot et al., 1991] (MIM 200900). The patient had neutropenia (900 cells/mm$^3$) and undetectable IgG2 and IgA. Other immunoglobulin levels were normal.

TABLE I. Syndromes Associated With Growth Deficiency*

| Name | Inheritance | Associated manifestations | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| A. Disproportionate short stature | | | | | |
| 1. Short limb skeletal dysplasia, type 1 | AR | Metaphyseal dysplasia, bowed femurs; may be seen with adenosine deaminase deficiency or Omenn syndrome (dermatitis, eosinophilia, progressive hepatosplenomegaly) | T, B | 12 | 12 |
| 2. Short limb skeletal dysplasia, type 2 | AR | McKusick type cartilage hair hypoplasia; metaphyseal dysplasia, mild leg bowing, fine/sparse hair | T, Ph | >100 | >70 |
| 3. Short limb skeletal dysplasia, type 3 | ?AR | Metaphyseal dysplasia, recurrent infection in male and female siblings | B | 2 | 2 |
| 4. Shwachman syndrome | AR | Metaphyseal dysplasia, exocrine pancreatic insufficiency, cyclic neutropenia | B, Ph | >150 | >150 |
| 5. Schimke immunoosseous dysplasia | AR | Spondyloepiphyseal dysplasia, progressive nephropathy, episodic lymphopenia, pigmentary skin changes | T | 10 | 10 |
| B. Proportionate short stature | | | | | |
| 1. Braegger syndrome | ? | IUGR, ischiadic hypoplasia, renal dysfunction, craniofacial anomalies, postaxial polydactyly, hypospadias, microcephaly, mental retardation | B | 1 | 1 |
| 2. Shokeir syndrome | AR | Absent thumbs, anosmia, ichthyosiform dermatosis, congenital heart defect; 3 sibships | T, B, Ph | 9 | 9 |
| 3. Fleisher syndrome | XL | Hypogammaglobulinemia, isolated growth hormone deficiency | B | 8 | 8 |
| 4. Toriello syndrome | ?AR | Prenatal growth deficiency, delayed skeletal maturation, cataracts, enamel hypoplasia, neutropenia, microcephaly, mental retardation | B, Ph | 2 | 2 |
| 5. Mulvihill-Smith syndrome | ?AD | Prenatal growth deficiency, microcephaly, broad forehead, small face, micrognathia, premature aging, multiple nevi, mental retardation | T, B | 6 | 4 |
| 6. Mulibrey nanism | AR | Prenatal growth deficiency, muscle weakness, abnormal sella turcica,hepatomegaly, ocular fundi lesions | B | >25 | 1 |

* AR = autosomal recessive, XL = X-linked, AD = autosomal dominant, ? = uncertain, T = T cells, B = B cells, Ph = phagocytes, IUGR = intrauterine growth retardation.

No mature CD20$^+$ B cells were detected, although less mature CD19$^+$ B cells were present in normal numbers. T cell levels were slightly decreased. Response to phytohemagglutinin (PHA) and alloantigen were low.

Several reports have described Type 1 short-limb skeletal dysplasia in conjunction with Omenn-like features, including alopecia, eosinophilia, ichthyosiform skin lesions, reticuloendotheliosis, and erythroderma [MacDermot et al., 1991; Schofer et al., 1991; Gatti et al., 1969; Gotoff et al., 1972]. Immune abnormalities include lymphopenia, absence of isohemagglutinins and specific antibody, decreased lymphoproliferative responses to mitogens, and panhypogammaglobulinemia. Adenosine deaminase and purine nucleoside phosphorylase activity are normal. Bone marrow and lymph nodes showed predominance of reticular cells and histiocytes and increased frequency of eosinophils. Many of the characteristics of Omenn syndrome are similar to those found in graft-vs.-host disease, and the diagnosis may be difficult to make with certainty. Thus, some of the reported cases of Omenn syndrome occurring with skeletal dysplasia may not be appropriate. Further discussion of the characteristics of Omenn syndrome may be found in the section on dermatological disorders.

***Cartilage-hair hypoplasia (CHH; MIM 250250).*** Also known as metaphyseal chondrodysplasia, McKusick type, CHH makes up Type 2 short-limb skeletal dysplasia. The syndrome is marked by short-limb dwarfism, metaphyseal chondrodysplasia, and fine sparse hair (Fig. 1). Immunological abnormalities are frequent but inconstant in this condition. Recurrent respiratory tract infections occur in 35% while severe varicella infection occurs in 11% [van der Burgt et al., 1991]. The recurrent infections tend to resolve by adulthood, despite persistence of immunological abnormalities. Lymphopenia (75%), neutropenia (15%), and decreased lymphoproliferative responses (87%) are also characteristic. Humoral immunity is nearly always normal (98%). The abnormalities in T cell number and function vary greatly. T cell number may be reduced, and lymphoproliferative responses to PHA, alloantigen, and tetanus toxoid are decreased [van der Burgt et al., 1991], as is cytotoxic activity [Pierce et al., 1983]. The macrophages have normal accessory function [Pierce and Polmar, 1982]. The impaired response of T cells could not be bypassed by chemical activators (calcium ionophore or phorbol myristate acetate), indicating that the T cells had an intrinsic defect distal to the initial activation sequence [Pierce and Polmar, 1982]. Natural killer cell (NK) activity is intact [Pierce et al., 1983]. Bone marrow transplantation corrected the immune dysfunction in one patient [Hong, 1989]. The condition is autosomal recessive and the gene has been mapped to 9p21–p13 [Sulisalo et al., 1994].


Fig. 1. **A:** This girl with cartilage-hair-hypoplasia (CHH) at age 4 years (top) had fine/sparse hair and short stature. Her fingers were short with square tips and "telescoping" of joints. At age 8 years (bottom), knee films showed irregular scalloped metaphyses. She did not suffer from severe infections, and T cell response to mitogens was normal. Intact T cell immunity in CHH is unusual but has been reported. **B:** This 11-month-old boy with CHH presented with recurrent infection and poor response to vaccines. He also had hepatosplenomegaly and fine/thin hair. Knee films at age 5 years show scalloping of the metaphyses. Immune findings were typical for patients with CHH: T cell proliferation in response to mitogens was reduced.

***Short-limb skeletal dysplasia with humoral immunodeficiency.*** Type 3 short-limb skeletal dysplasia was described in two sibs [Ammann et al., 1974]. Immunoglobulin levels were low (IgG 100 mg/dl, IgM 5, IgA 5). T cell number, response to PHA, and delayed type hypersensitivity (DTH) tests were normal; however, T cell response in the mixed leukocyte culture (MLC) was decreased. Complement activity was normal. Ingestion and killing by phagocytes were normal in the presence of normal serum, but decreased with the patient's serum, suggesting the presence of an inhibitory factor in the patient's serum.

***Shwachman syndrome (MIM 260400).*** This condition presents with pancreatic insufficiency, pancytopenia, and metaphyseal dysostosis. The patients also have a predisposition to malignancy. Recurrent respiratory, cutaneous, and systemic infections are characteristic [Aggett et al., 1980]. Defective neutrophil mobility (30% of control for both resting and stimulated neutrophils) is a constant finding and may contribute to the increased susceptibility to infection [Aggett et al., 1979]. No correlation exists between mobility and neutrophil count. Nitroblue tetrazolium (NBT) dye reduction is normal. Decreased IgA and IgM were each found in 14% of patients, while B cell numbers were normal [Aggett et al., 1979]. T cell numbers were low in 14% and PHA response was decreased in 7%. Neutrophils from affected individuals were found to have an unusual morphologic response (patching) of the cell surface [Rothbaum et al., 1982]. This pattern may reflect defective cytoskeletal structure or function and be associated with defective chemotaxis. A generalized defect in cytoskeletal function might also contribute to the bony and pancreatic abnormalities in this syndrome.

***Schimke immunoosseous dysplasia (MIM 242900).*** These patients have short trunk skeletal dysplasia, lentigenes, and glomerulonephritis with immune-complex formation [Schimke et al., 1974]. A broad and depressed nasal bridge with a bulbous nasal tip is characteristic (Fig. 2). Patients are prone to viral and bacterial infections [Ludman et al., 1993; Spranger et al., 1991]. Lymphopenia, primarily affecting CD4 cells, is present. T cell response to mitogen is reduced to 3–50% of normal, and DTH test responses are absent. An increased percentage of peripheral T cells express the gamma/delta T cell receptor or both the CD4 and CD8 antigens [Spranger et al., 1991], implying disordered T cell maturation. B cell number and activity are normal. Decreased IgG level is secondary to proteinuria. NK number is normal.

## Proportionate Short Stature

***Braegger syndrome (MIM 243340).*** A boy born to consanguineous parents had ischiadic hypoplasia, micro-

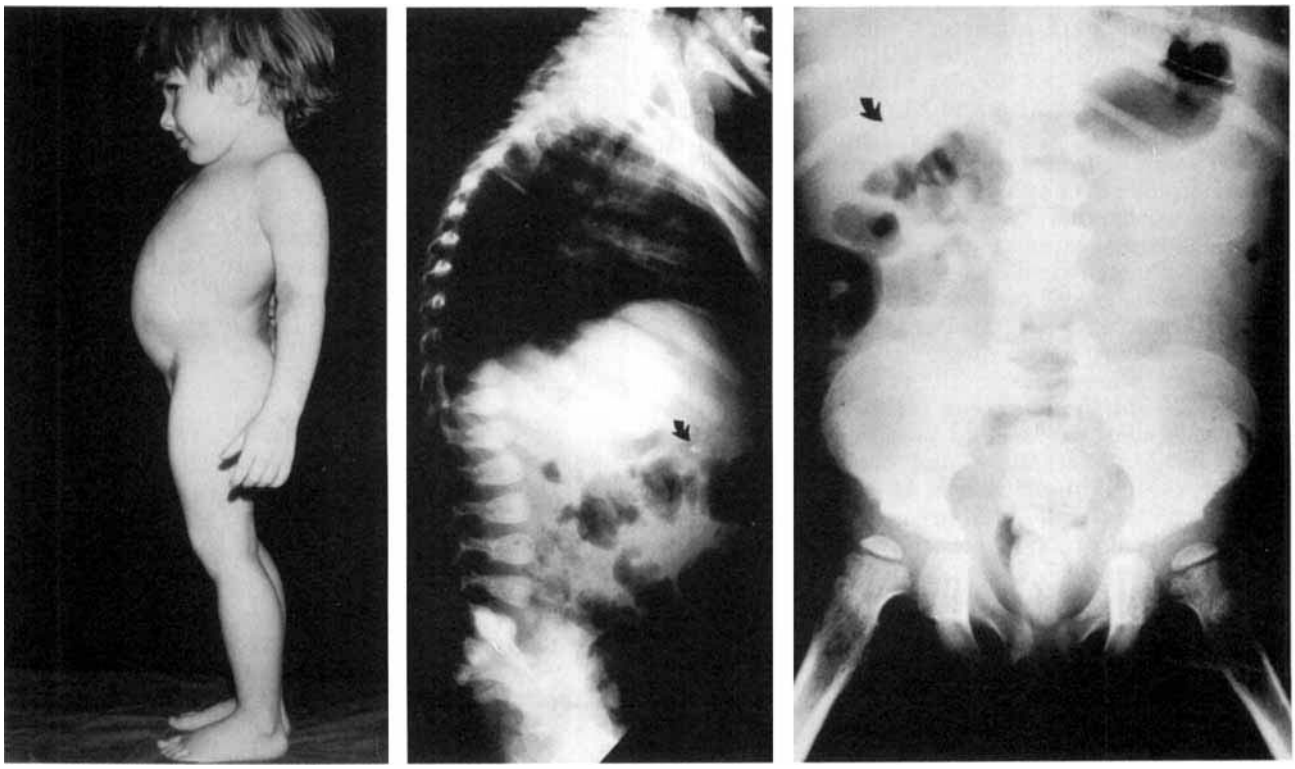

Fig. 2. This 4 yr. 6 mo. girl with Schimke immuno-osseous dysplasia had progressive renal disease, disproportionate growth deficiency with a short trunk, upslanting palpebral fissures, broad nasal bridge, and bulbous nasal tip. Abdominal films show lordosis with flat and anteriorly rounded vertebral bodies with demineralization of bones. Small capital femoral epiphyses with lateral subluxation and slanted acetabular roofs are present. A gallstone is present (arrows; published with permission from Ludman et al. [1993], Am J Med Genet 47:793–796). This patient had leukopenia, lymphopenia, and decreased T cell number.

cephaly, renal dysfunction, cryptorchidism, postaxial syndactyly, conductive hearing loss, and recurrent respiratory infections [Braegger et al., 1991]. Decreased IgG (280 mg/dl) and IgM (23 mg/dl) were present. IgA, isohemagglutinins, and anti-diphtheria antibodies were not detectable. Complement, T cell, and phagocyte studies were normal.

***Shokeir syndrome (MIM 274190).*** Nine individuals from three sibships with absent thumbs, proportionate short stature, anosmia, ichthyosiform dermatosis, and recurrent infection were reported [Shokeir et al., 1978]. One kindred had cardiac defects. Increased susceptibility to bacterial, viral, and fungal infections, especially mucocutaneous candidiasis, was present. Hypogammaglobulinemia (IgG 400–560 mg/dl, IgM 10–25 mg/dl) was variable, with depressed or absent IgA being the most constant abnormality. T cell response to PHA stimulation was decreased. Neutropenia was present. ADA and purine nucleoside phosphorylase (PNP) levels were normal.

***Growth hormone deficiency with X-linked agammaglobulinemia (MIM 307200).*** Affected individuals have recurrent sinopulmonary infections, short stature, and decreased growth hormone levels without other endocrine abnormalities [Fleisher et al., 1980]. Both in vivo specific antibody production and in vitro immunoglobulin production are decreased to absent. B cell number, IgG, IgM, and IgA are greatly decreased or absent, consistent with X-linked agammaglobulinemia (XLA) [Conley et al., 1991]. T cell number and function were normal. Linkage studies were consistent with localization of XLA/growth hormone deficiency (GHD) at or near the XLA locus at Xq21–q22 [Conley et al., 1991]. At present, it is unknown if XLA and XLA/GHD are distinct linked loci or allelic variations of a single locus, or if XLA/GHD results from a contiguous gene deletion. The growth hormone gene is located on chromosome 17.

***Toriello syndrome.*** Two sisters with prenatal-onset growth deficiency, cataracts, microcephaly, mental retardation, enamel hypoplasia, generalized delay of ossification, and recurrent respiratory infections were described [Toriello et al., 1986]. They had decreased IgM and IgG, and neutropenia during infections. The elder girl died from pneumonia.

***Mulvihill-Smith syndrome (MIM 176690).*** This condition is characterized by premature aging, pigmented nevi, microcephaly, and ocular and dental anomalies [Mulvihill and Smith, 1975] (Fig. 3). An affected woman who suffered from respiratory infections, otitis media, and papilloma virus infections had slightly decreased IgG (611 mg/dl) and IgA (41 mg/dl), with normal B cell number [Ohashi et al., 1993]. T cell response to PHA was 8% of control, with normal T cell, CD4 cell, and CD8 cell numbers. Another patient had severe viral infections and intermittent lymphopenia affecting T cells and B cells, increased IgM and IgE, and a decreased response to PHA [Bartsch et al., 1994]. IgG levels were low in two other patients [Mulvihill and Smith, 1975; Baraitser et al., 1986]. Some patients do not have a history of recurrent infections.

***Mulibrey nanism (MIM 253250).*** This is a syndrome of prenatal-onset growth failure, muscular hypotonia, hepatomegaly, long and shallow sella turcica, retinal abnormalities, and constrictive pericarditis. Such individuals may suffer from frequent infections. One affected patient had both isolated growth hormone deficiency and low IgG (especially IgG2 and IgG4), IgE, and IgM [Haraldsson et al., 1993]. Total B cell number was low. Kappa/lambda light chain ratios for IgG, IgA, and IgM were abnormal. T cell function and number were normal.

## SYNDROMES ASSOCIATED WITH SPECIFIC ORGAN SYSTEM DYSFUNCTION

Immunodeficiency may also exist in certain individuals with defects primarily affecting a single organ sys-

Fig. 3. This 7 yr. 7 mo. girl (CCFA #3228) with short stature, small face, micrognathia, and multiple nevi was diagnosed with Mulvihill-Smith syndrome (**top**). Subsequent photos show her appearance at 10 yr. 11 mo. (**middle**) and 13 yr. 1 mo. (**bottom**). Skull films at age 8 yr. 7 mo. show marked arrest of facial growth and micrognathia (published with permission from Wong et al. [1979], Cleft Palate J 16:286–290). Although immune studies were not performed in this patient, decreased T cell response to mitogens and dysgammaglobulinemia have been reported.

tem. We describe syndromes affecting the gastrointestinal tract, nervous system, and skin, that are also associated with decreased immune function.

## Gastrointestinal Syndromes

Gastrointestinal abnormalities may lead to malnutrition and secondarily result in an immunodeficient state; however, in the syndromes described here, signs and symptoms of immunodeficiency precede nutritional deprivation. Thus, the immune defects are specific features of each condition (Table II).

***Familial intestinal polyatresia (MIM 243150).*** This unusual syndrome is marked by atretic lesions occurring throughout the gastrointestinal tract. Severe combined immunodeficiency was described in three affected brothers [Moreno et al., 1990]. Although B cell numbers were normal, levels of IgG (<42 mg/dl), IgA (<7 mg/dl), IgM (<20 mg/dl), and IgE (18 IU/ml) were decreased. T cells made up less than 1% of lymphocytes and did not respond to PHA. ADA activity was normal. Since the recurrent infections occurred early in life while the patients still retained good nutritional status, they were not thought to be secondary to the intestinal problems. Whether this phenotype is a variant of familial intestinal polyatresia or is a distinct entity with some clinical overlap is unclear.

***Powell syndrome (MIM 304930).*** Eight males in three generations had intractable diarrhea, polyendocrinopathy (diabetes mellitus, thyroid autoimmunity), fatal infection, eczema, and hemolytic anemia [Powell et al., 1982]. Eleven other males in the kindred died in early childhood from infection or shortly after immunization with live viral agents. Immune abnormalities were inconsistent and relatively mild. Autoantibodies (anti-thyroid, anti-smooth muscle, or anti-nuclear antibodies) were found in two other children and increased numbers of activated T cells were found [Shigeoka et al., 1993]. The gene has been mapped near the Wiskott-Aldrich locus on the X chromosome at Xp11.2 [Shigeoka et al., 1993].

***Sclerosing cholangitis (MIM 242850).*** Record et al. [1973] described a girl with frequent infections with encapsulated organisms and intrahepatic sclerosing cholangitis. She had dysgammaglobulinemia with slightly decreased IgA, very low IgM, high IgG, and low isohemagglutinin titers. She had a normal DTH response but a suboptimal response to PHA. Four other relatives died of overwhelming sepsis and two of them also had sclerosing cholangitis. A 10-month-old boy with primary sclerosing cholangitis had decreased IgG, IgA, and B cell number [Naveh et al., 1983]. T cell numbers and response to PHA were normal. His brother died of fulminant infection.

***Primary intestinal lymphangiectasia (MIM 152800).*** This condition is marked by lower limb edema and intestinal loss of protein. Both immunoglobulin and lymphocytes may be lost leading to hypogammaglobulinemia and lymphopenia. Such patients have decreased response to mitogen and allogeneic cells (22–39% of normal) [Weiden et al., 1972]. Decreased in vitro lymphocyte responsiveness was correlated with low serum albumin levels. In response to mitogen, lymphocytes obtained from chylous effusions proliferated more than did peripheral blood lymphocytes. Loss of recirculating, long-lived lymphocytes into the gastrointestinal tract could result in a relative depletion of those lymphocytes required for proliferation in response to mitogen. This condition is an autosomal dominant trait.

***Enteropathy with villous edema (MIM 600351).*** Individuals with this condition have paroxysmal bouts of life-threatening gastroenteritis with large losses of plasma-like stools [Smith et al., 1994]. Mild IgG2 deficiency with normal plasma cell number is usually present. Massive protein and neutrophil loss occurs. Edematous jejunal villi with defective basement membrane but without significant inflammatory infiltrate is characteristic. This syndrome appears to be an autosomal dominant trait.

## Dermatologic Syndromes

While dermatologic symptoms such as dermatitis or skin infection often occur in immune deficient patients, some immunodeficiency syndromes present with primarily cutaneous manifestations (Table III).

***Dyskeratosis congenita (MIM 305000).*** This condition is marked by cutaneous pigmentation, nail dys-

TABLE II. Syndromes Associated With Specific Organ System Dysfunction: Gastrointestinal Syndromes*

| Name | Inheritance | Associated manifestations | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Familial intestinal polyatresia | ? | Multiple atresias from pylorus to rectum with combined immunodeficiency; three brothers | T, B | 21 | 3 |
| 2. Powell syndrome | XL | Intractable diarrhea, autoimmune polyendocrinopathy, eczema, hemolytic anemia | T, B | 19 | 7 |
| 3. Primary sclerosing cholangitis with immunodeficiency | ?AR | Intrahepatic sclerosing cholangitis, frequent infections | B | 4 | 4 |
| 4. Primary intestinal lymphangiectasia | AD | Lower limb edema, loss of immunoglobulin and lymphocytesinto GI tract | T, B | >300 | >290 |
| 5. Enteropathy with villous edema | AD | Fulminant plasma-like stools, edematous jejunal villi; in Mennonites | B, Ph | 32 | >16 |

* See Table I for definitions of abbreviations.

TABLE III. Syndromes Associated With Specific Organ System Dysfunction: Dermatological Syndromes

| Name | Inheritance | Associated manifestations | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Dyskeratosis congenita | XL, AR, AD | Atrophy and pigmentation of skin, nail dystrophy, leukoplakia of oral mucosa | T, B, Ph | >190 | >70 |
| 2. Chediak-Higashi syndrome | AR | Partial albinism, anemia, leukopenia, atypical lymphoproliferative syndrome, giant cytoplasmic granules in leukocytes, neuropathy, hepatosplenomegaly | Ph | >200 | >200 |
| 3. Griscelli syndrome | AR | Partial albinism, frequent pyogenic infections, lymphohistiocytosis, episodic neutropenia/thrombocytopenia | T, B Ph | 10 | 10 |
| 4. Kotzot syndrome | AR | Tyrosinase-positive oculocutaneous albinism, granulocytopenia, thrombocytopenia, recurrent bacterial infections, microcephaly, mental retardation | Ph | 2 | 2 |
| 5. Netherton syndrome | AR | Trichorrhexis invaginata (bamboo hair), ichthyosiform dermatitis, atopic diathesis | B | 43 | 8 |
| 6. Acrodermatitis enteropathica | AR | Vesiculobullous dermatitis, alopecia, diarrhea; due to zinc deficiency | T, B, Ph | >170 | >30 |
| 7. Wiskott-Aldrich syndrome | XL | Severe eczematous dermatitis, thrombocytopenia, bloody diarrhea, recurrent infection | T, B | >300 | >300 |
| 8. Omenn syndrome | AR | Erythematous maculopapular dermatitis, eosinophilia, hepatosplenomegaly, lymphadenopathy, phagocytosis of blood cells | T, B, Ph | >20 | >20 |
| 9. Papillon-Lefevre syndrome | AR | Palmar/plantar hyperkeratosis, precocious periodontal disease | T, Ph | >200 | 4 |
| 10. Jung syndrome | ? | Pyoderma, folliculitis, atopic dermatitis, response to histamine-1 antagonist | T, B, Ph | 3 | 3 |

* See Table I for definitions of abbreviations.

trophy, leukoplakia of the oral mucosa, aplastic anemia and an increased risk of malignancy. Neutropenia secondary to bone marrow failure occurs in approximately 40% of patients [Drachtman and Alter, 1992]. Opportunistic infections, including cytomegalovirus and Pneumocystis, have been reported. Immunoglobulin abnormalities are inconstant, but have included panhypogammaglobulinemia, decreased IgG and IgM, isolated decreased IgM, and increased IgG [Womer et al., 1983]. Thymic aplasia and cellular depletion of the spleen and lymph nodes were reported in two patients [Trowbridge et al., 1977]. Absent DTH and impaired responses to PHA and alloantigen may also be present [Womer et al., 1983]. The gene has been mapped to Xq28 [Arngrimsson et al., 1993].

***Chediak-Higashi syndrome (MIM 214500).*** In this well-defined primary immunodeficiency, patients present with recurrent bacterial infections, partial oculocutaneous albinism, prolonged bleeding time, nystagmus, and neuropathy (Fig. 4). They are susceptible to an atypical lymphoproliferative syndrome. Giant cytoplasmic granules in leukocytes and platelets are diagnostic. The patients have normal phagocytosis, but the rate of killing is slowed and chemotaxis is decreased [Root et al., 1972]. The large granules remain intact during phagocytosis and appear to integrate into the phagocytic vacuole, but do not discharge their contents. Phagocytic cell oxygen formation, hydrogen peroxide formation, hexose monophophate shunt activity, and respiratory burst are normal. Decreased NK activity has been described [Haliotis et al., 1980]. Two neutrophil proteins involved in killing, cathepsin G and elastase, are deficient in the patients [Ganz et al., 1988]. Defective NK function and decreased amounts of cathepsin G and elastase have been described in the beige mouse, the murine analogue of Chediak-Higashi [Roder and Duwe, 1979; Takeuchi et al., 1986].

***Griscelli syndrome (MIM 214450).*** A syndrome of partial albinism, acute episodes of fever, neutropenia and thrombocytopenia, and lymphohistiocytosis was described by Griscelli et al. [1978] in two unrelated patients. Pigmentary dilution was due to accumulation of melanosomes in melanocytes. The patients suffered from fungal, viral, and bacterial infections. The absence of giant granules differentiates this condition from Chediak-Higashi. The patients showed decreased levels of IgA (8–81 mg/dl) and IgG (250–525 mg/dl) and absent DTH reaction to a variety of antigens. Pokeweed mitogen (PWM) failed to stimulate immunoglobulin secretion. Coculture of normal T cells with the patient's B cells resulted in immunoglobulin production, while coculture of the patient's T cells with normal B cells did not lead to immunoglobulin production, implying a T helper cell defect. Although proliferation in response to alloantigen was normal, generation of cytotoxic cells was not observed. T and B cell numbers and response to PHA and concanavalin A (ConA) were normal. Neutrophil chemotaxis and NBT dye reduction were normal. Bactericidal activity of granulocytes was moderately decreased. Response to PHA was normal. Bone marrow transplantation corrects the immunologic abnormalities and results in an infection-free state [Schneider et al., 1990].

***Kotzot syndrome (MIM 203258).*** A brother and sister of two related sets of consanguineous parents had tyrosinase-positive oculocutaneous albinism, inter-

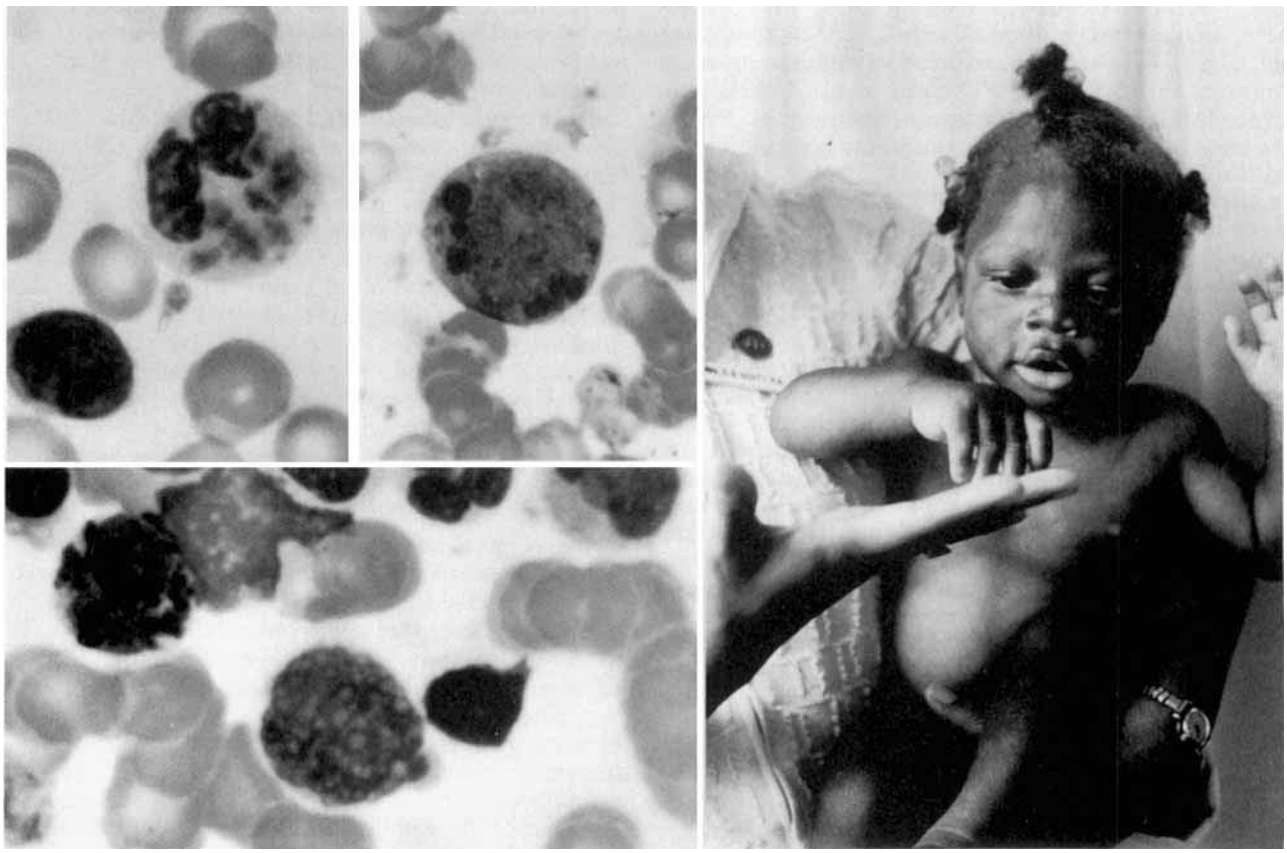

Fig. 4. This young African-American girl displayed hypopigmentation and immunodeficiency. Her leukocytes contained giant granules, diagnostic for Chediak-Higashi syndrome. Affected individuals usually have defective neutrophil chemotaxis and killing and decreased natural killer cell activity.

mittent thrombocytopenia, microcephaly, rough and projecting hair, and mild mental retardation [Kotzot et al., 1994]. They also had a protruding midface, thin upper lip, and nystagmus. Bleeding time was prolonged with decreased Factor XIII and antithrombin III. Granulocytopenia was as low as 120 cells/mm$^3$, resulting in recurrent bacterial infections. Giant granules were not present. B, T, neutrophil, and NK functions were normal.

***Netherton syndrome (MIM 256500).*** The triad of trichorrhexis (brittle hair), ichthyosiform erythroderma, and atopic diathesis has been designated the Netherton syndrome. Recurrent infections occur in 28%, with IgG abnormalities (both hypo- and hyper-IgG) present in 14% [Greene and Muller, 1985]. Impaired DTH and mitogen responses can occur. Another patient had increased IgE and markedly delayed neutrophil phagocytosis. This disorder is inherited in an autosomal recessive fashion.

***Acrodermatitis enteropathica (MIM 201100).*** This condition is characterized by diarrhea, vesiculobullous dermatitis, and alopecia. Severe infection with opportunistic pathogens is frequent. The condition is autosomal recessive and due to defective intestinal zinc metabolism. All abnormalities resolve after normalization of serum zinc levels. Decreased response to PHA was found in 6 of 8 patients studied, and DTH was decreased in 5 of the 8 patients [Chandra, 1980]. Hypogammaglobulinemia may be variably present [van Wouwe, 1989]. Defective chemotaxis of neutrophils (57% of normal) and monocytes (25–30% of normal) was demonstrated in three affected patients [Weston et al., 1977]. Autopsy findings have included atrophic thymus, tonsils, germinal centers, and Peyer's patches [Chandra, 1980].

***Wiskott-Aldrich syndrome (MIM 301000).*** This well-defined X-linked primary immunodeficiency is characterized by chronic eczema, thrombocytopenia (with small, defective platelets), and recurrent infection with encapsulated organisms leading to potentially fulminant pneumonia, meningitis, and septicemia. Immunoglobulin levels can be highly variable due to increased rate of both synthesis and breakdown [Blaese et al., 1971]. Typically, IgG is normal or elevated, IgM is decreased, IgA and IgE are increased, isohemagglutinins are decreased, and there is failure to produce antibodies in response to polysaccharide antigen and viral agents [Standen, 1991]. Later in the disease, there may be reduced numbers of T cells with decreased responses to mitogen and alloantigen with

anergy to skin testing. NK cell number may be increased. In affected individuals, the lymphocyte surface molecule CD43 is absent, reduced in number, or in an abnormal form [Remold-O'Donnell et al., 1987]. This may reflect impaired glycosylation [Molina et al., 1992]. The gene for Wiskott-Aldrich syndrome has been localized to Xp11.22–p11.23 [Derry et al., 1994].

***Omenn syndrome (MIM 267700).*** Omenn disease presents with erythematous and maculopapular skin rash, eosinophilia, reticulosis, hepatomegaly, and lymphadenopathy. The combined immunodeficiency leads to chronic diarrhea, recurrent infection, and premature death. Although discussed previously in the context of short-limb skeletal dysplasia, it most frequently occurs without associated growth deficiency. The immune dysfunction is very variable. CD4 cell count may be decreased [Karol et al., 1983]. Lymphoid tissues contain a relative paucity of lymphocytes with diffuse proliferation of histiocytes. Thymic hypoplasia has also been reported. T cell numbers are normal, but their proliferation in response to PHA and allogeneic cells are often <5% of control. Skin tests are negative and IL-2 production is defective [Businco et al., 1987]. B cell number may be decreased (1% of lymphocytes) and proliferation in response to PWM is also low [Karol et al., 1983]. Hypogammaglobulinemia, especially affecting IgG and IgA, may occur. Elevated IgE (up to 4,800 IU/ml) is also found [Businco et al., 1987]. Phagocytic function is normal. ADA is normal. Bone marrow transplantation can lead to immune recovery [Stephan et al., 1993]. Because of the clinical similarity to graft-vs.-host disease, it has been hypothesized that Omenn syndrome might be secondary to maternal T cell engraftment. However, recent studies have failed to demonstrate maternal/fetal transfer of T cells [Stephan et al., 1993]. Thus, the pathogenesis of Omenn syndrome remains unclear. This appears to be an autosomal recessive trait. The diagnosis of Omenn syndrome may be difficult to make with certainty. The Omenn syndrome phenotype may not be a specific syndrome, but instead might be etiologically heterogeneous.

***Papillon-Lefevre syndrome (MIM 245000).*** In this condition, palmar-plantar hyperkeratosis and precocious periodontal disease leads to loss of primary and permanent teeth. Approximately 17% of cases are associated with infections other than periodontal disease [Van Dyke et al., 1984]. Furunculosis and pyoderma are the most frequent extra-oral infectious manifestations. Neutrophil chemotaxis and random movement are both decreased. Decreased proliferation in response to PHA has been described. The IgG level may be mildly elevated or normal.

***Jung syndrome (MIM 146840).*** A father and son had recurrent pyoderma, folliculitis, corneal ulcerations, and atopic dermatitis [Jung et al., 1983]. The child's grandfather had a similar history. T cell responses to PHA, *Candida,* and tetanus toxoid were reduced. PWM-induced immunoglobulin production was decreased to 37% of control. IgE was increased (367–632 IU/ml). Phagocytes showed defective bactericidal activity (50% of normal) with normal chemotaxis and NBT reduction. The immune abnormalities and clinical manifestations improved after treatment with the histamine-1 antagonist chlorpheniramine, and the abnormalities recurred after the agent was withdrawn.

## Neurologic Syndromes

Neurological abnormalities ranging from structural abnormalities to epilepsy or ataxia have been reported in association with immunodeficiency (Table IV).

***Ritscher-Schinzel syndrome (MIM 220210).*** Two sisters with Dandy-Walker-like malformation (cerebellar hypoplasia and posterior fossa cyst malformation), craniofacial anomalies, and atrioventricular septal defects were reported [Ritscher et al., 1987]. One sister died after unsuccessful cardiac surgery. Immune abnormalities were demonstrated in the surviving sister [Lauener et al., 1989]. All IgG subclass levels were decreased. Antibodies to polysaccharide antigens were not detected, but those to protein antigens were normal. B and T cell numbers, proliferative responses to mitogen and antigen, and skin tests were normal.

***Vici syndrome (MIM 242840).*** A syndrome of agenesis of the corpus callosum, bilateral cataracts, seizures, cleft lip/palate, cerebellar hypoplasia, and cutaneous hypopigmentation was described in two brothers [Vici et al., 1988]. Both suffered from recurrent respiratory infections (both died from pneumonia) and chronic mucocutaneous candidiasis. In one brother, autopsy showed hypoplasia of the thymus and depletion of T-dependent areas of lymph nodes. He had decreased CD4 T cell number and absent DTH responses. PHA-induced proliferation was normal. Serum IgG2 was selectively decreased. Isohemagglutinin titer was normal. NK activity was normal.

TABLE IV. Syndromes Associated With Specific Organ System Dysfunction: Neurological Syndromes*

| Name | Inheritance | Associated findings | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Ritscher-Schinzel syndrome | AR | Dandy-Walker-like malformation, atrioventricular canal defect,short stature; 2 sisters | B | 5 | 1 |
| 2. Vici syndrome | ? | Agenesis of corpus callosum, cleft lip, cutaneous hypopigmentation, bilateral cataracts; 2 brothers | T, B | 2 | 2 |
| 3. Krawinkel syndrome | ? | Lissencephaly, abnormal lymph nodes, spastic tetraplegia,transient arthritis, mental retardation | T, B Ph | 1 | 1 |

* See Table I for definitions of abbreviations.

***Krawinkel syndrome.*** A boy with lissencephaly, spastic tetraplegia, transient arthritis, psychomotor retardation, and abnormal lymph nodes suffered from recurrent bacterial and mycotic infections [Krawinkel et al., 1989]. T cell proliferation was reduced in response to PHA or allogeneic cells, and DTH response was absent. Serum immunoglobulin levels were normal, but no antibody production occurred in response to immunization with tetanus toxoid, a T cell-dependent antigen. PWM-induced differentiation of B cells was normal after addition of T cells from a normal donor but did not occur with the patient's T cells, indicating a T cell-mediated immune defect. No germinal centers were found on lymph node biopsy. Two months prior to death, responses to PHA and allogeneic cells were normal. ADA and PNP levels were normal.

## MISCELLANEOUS SYNDROMES

The immunodeficiencies discussed in this section are associated with extraimmune manifestations not addressed previously (Table V).

***Frenkel-Russe syndrome (MIM 267900).*** A 13-year-old boy with retinal telangiectasias who suffered from recurrent respiratory infections and meningitis refractory to antibiotics [Frenkel and Russe, 1967] had decreased IgG (350 mg/dl) and undetectable IgA and IgM. DTH response was absent. Bone marrow aspirate showed no plasma cells. His sister had less extensive telangiectasias and showed impaired DTH response although immunoglobulin levels were normal.

***Lichtenstein syndrome (MIM 246550).*** Lichtenstein [1972] described monozygous twins with facial anomalies ("carp mouth," anteverted nostrils, synophrys), skeletal anomalies (peripheral osteoporosis, failure of fusion of posterior spinal arches) and giant lung cysts. The patients had recurrent infections, including pneumonia and joint abscess, with neutropenia (less than 1,500 neutrophils/$mm^3$). IgG and IgM levels were normal. Bone marrow was hypocellular with a decrease in myeloid precursors.

***Good syndrome.*** Immunodeficiency with thymoma is most commonly seen between the ages of 40 and 70. Recurrent infections, hypogammaglobulinemia, and decreased B cells are the most consistent findings, although impaired cellular immunity does occur. A pediatric case was reported in an 8-year-old boy [Watts and Kelly, 1990]. Lymphopenia (<1,000 cells/$mm^3$) and decreased IgG (246 mg/dl), IgM (24 mg/dl), and IgA (10 mg/dl) were found after thymectomy. T cell number was greatly decreased. The patient died of disseminated varicella.

## MALFORMATION SYNDROMES WITH OCCASIONAL IMMUNODEFICIENCY

There are several well-established malformation syndromes in which immunodeficiency has been identified in some patients (Table VI). In many cases, immune studies have been carried out on only a few individuals. In these syndromes, it is unclear if the rare occurrences of immunodeficiency are coincidental or actually occur with some frequency in affected individuals. It is possible that additional individuals would be found to have immune defects if such tests were conducted on more patients. Perhaps one end of the spectrum of each condition is associated with immunodeficiency, with most individuals possessing intact immune systems. A contiguous gene deletion extending beyond the area necessary to produce the syndrome could cause the immunodeficiency. In many of these conditions, frequent infections may occur, but it is not clear if this is due to true immune defects. In general, frequent infection is not a frequent clinical manifestation of these conditions.

Immune dysfunction has been described in Schwartz-Jampel syndrome [Mollica et al., 1979; Kirschner and Parkman, 1976], Rubinstein-Taybi syndrome [Rivas et al., 1980; Kimura et al., 1993], Dubowitz syndrome [Kuster and Majewski, 1986], Smith-Lemli-Opitz syndrome [Ostergaard et al., 1992], Hutchinson-Gilford syndrome [Harjacek et al., 1990], Hallerman-Streiff syndrome [Chandra et al., 1978], Seckel syndrome [Lilleyman, 1984], and Menkes syndrome [Pedroni et al., 1975].

## INBORN ERRORS OF METABOLISM ASSOCIATED WITH IMMUNODEFICIENCY

Several metabolic defects are associated with immunodeficiency (Table VII). In most of these syndromes, it is unknown if the immunological deficit is due to block of a metabolic process important for immune function or if the build up of toxic metabolites adversely affects the cells. Most of the immunological abnormalities appear to be secondary to the metabolic derangement, since correction of the metabolic defect usually results in normal immune function.

***Adenosine deaminase (ADA) deficiency (MIM 102700).*** Perhaps the best-characterized metabolic defect associated with immunodeficiency is ADA deficiency. This syndrome may account for up to 50% of patients with autosomal severe combined immunodeficiency disease [Hirschhorn, 1993]. The ADA gene has been mapped to chromosome area 20q13-ter [Petersen et al., 1987]. Accumulation of deoxyadenosine and

TABLE V. Miscellaneous Syndromes*

| Name | Inheritance | Associated abnormalities | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Frankel-Russe syndrome | ?AR | Retinal telangiectasias, recurrent infections | T, B | 2 | 2 |
| 2. Lichtenstein syndrome | ? | Osteoporosis, bony anomalies, lung cysts, neutropenia; monozygotic female twins | B, Ph | 2 | 2 |
| 3. Good syndrome | ? | Immunodeficiency, thymoma | T, B | 1 | 1 |

* See Table I for definitions of abbreviations.

TABLE VI. Well-Recognized Syndromes With Immunodeficiency as an Occasional Feature*

| Name | Inheritance | Associated anomalies | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Schwartz-Jampel syndrome | AR | Epiphyseal dysplasia, short stature, myotonic myopathy, myopia,joint contractures | T, B | >50 | 2 |
| 2. Rubinstein-Taybi syndrome | ? | Broad thumbs and halluces, prominent nasal septum below ala nasi, cryptorchidism, mental retardation | T, Ph | >550 | 2 |
| 3. Dubowitz syndrome | ? | Prenatal-onset growth deficiency, microcephaly, eczematoid skin lesions, mental retardation | Ph | >40 | 3 |
| 4. Smith-Lemli-Opitz syndrome | AR | Cryptorchidism, partial syndactyly of 2nd and 3rd toes, anteverted nostrils; defect in cholesterol metabolism | Ph | >120 | 1 |
| 5. Hutchinson-Gilford syndrome | ?AD | Postnatal growth deficiency, alopecia, atrophy of subcutaneous fat, atherosclerosis | T, B | >100 | 1 |
| 6. Hallermann-Streiff syndrome | ?AD | Thin pinched nose, congenital cataracts, hypotrichosis, microphthalmia | B | >150 | 1 |
| 7. Seckel syndrome | ? | Bird-like facies, microcephaly, mental retardation | Ph | 20 | 2 |

* See Table I for definitions of abbreviations.

adenosine may lead to lymphocyte toxicity. The skeletal system is also affected, and radiologic findings include cupping and flaring of the costochondral junctions, platyspondylysis, thick growth arrest lines, and an abnormal bony pelvis. The degree of immunodeficiency is variable. Severe combined immunodeficiency may occur with complete functional absence of T cell and B cell immunity. Alternatively, only mild abnormalities of T and B cell function may occur.

***Purine nucleoside phophorylase (PNP) deficiency (MIM 164050).*** PNP is required for normal catabolism of purines. Many patients have neurologic symptoms including spasticity and mental retardation. Hemolytic anemia has also been described [Carapella-de Luca et al., 1978]. Recurrent infections are frequent. Decreased T cell numbers result in lymphopenia and cutaneous anergy. B cell numbers are generally normal and immunoglobulin levels and antibody formation are

TABLE VII. Inborn Errors of Metabolism*

| Name | Inheritance | Associated manifestations | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Adenosine deaminase deficiency | AR | Severe immunodeficiency, cupping and flaring of costochondral junctions | T, B | >80 | >80 |
| 2. Purine nucleoside phosphorylase deficiency | AR | Severe immunodeficiency, neurological findings, hemolytic anemia | T | >30 | >30 |
| 3. 5′-nucleotidase elevation | ? | Increased nucleotide catabolism, developmental delay, seizures, megaloblastic anemia, aggressive behavior | B | 1 | 1 |
| 4. Biotin-dependent multiple carboxylase deficiency | AR | Alopecia, developmental delay, hypotonia, seizures; biotinidase deficiency | T, B | >100 | 4 |
| 5. Transcobalamin II deficiency | AR | Transport protein for B12; severe megaloblastic anemia, leukopenia, thrombocytopenia | B, Ph | >40 | 7 |
| 6. Folic acid malabsorption (transport defect) | AR | Megaloblastic anemia, convulsions, movement disorder | T, B | 12 | 2 |
| 7. Glycogen storage disease Ib | AR | Recurrent infection, neutropenia; glucose-6-phosphate transport defect | Ph | >40 | >25 |
| 8. Alpha-mannosidosis | AR | Hepatosplenomegaly, psychomotor retardation, dysostosis multiplex | T, B, Ph | >60 | 5 |
| 9. Galactosemia | AR | Hepatomegaly, hypoglycemia, jaundice, feeding difficulties | Ph | >100 | 5 |
| 10. Glutathione synthetase deficiency | AR | Hemolytic anemia, acidosis, neutropenia; decreased bactericidal activity, failure to assemble microtubules | Ph | 16 | 2 |
| 11. Orotic aciduria, type I | AR | Megaloblastic anemia, severe infection | T | 13 | 3 |
| 12. Methylmalonic aciduria | AR | Acidosis, recurrent severe infection | T, B, Ph | >100 | 7 |
| 13. Propionic acidemia | AR | Acidosis, vomiting, ketosis | B | >100 | 2 |

* See Table I for definitions of abbreviations.

intact. However, a few patients have been reported with poor B cell function [Markert et al., 1987].

***Page syndrome.*** A 3-year-old girl with recurrent sinusitis, developmental delay, seizures, megaloblastic anemia, and aggressive behavior was found to have increased catabolism of purine and pyrimidine nucleotides [Page et al., 1991]. Folic acid and $B_{12}$ levels were normal. IgG level was low to borderline. The catabolism of nucleotides was increased 10- to 30-fold. 5′-nucleotidase activity was increased. It is unknown if the increased nucleotidase activity is primary or is in response to abnormal amounts of an as yet unidentified nucleotide. Oral nucleotide supplementation resulted in improved behavior and improvement in symptoms.

***Multiple carboxylase deficiency (MIM 252170).*** This condition is due to defects in biotin metabolism. Symptoms include seizures, hypotonia, ataxia, hearing and visual loss, developmental delay, dermatitis, alopecia, and recurrent candidiasis. Two siblings had absent skin test responses but normal T cells responses to alloantigen and PHA [Cowan et al., 1979]. One had decreased IgA and poor antibody response to pneumococcal vaccine. In other cases of biotinidase deficiency, no immunodeficiency is present [Sweetman and Nyhan, 1986]. Biotin deficiency in an animal model has been associated with decreased B and T cells [Sweetman and Nyhan, 1986].

***Transcobalamin II deficiency (MIM 275350).*** A reduction of the primary serum transport protein for vitamin $B_{12}$ leads to severe megaloblastic anemia, failure to thrive, diarrhea, vomiting, and lethargy. Hypogammaglobulinemia is frequently present, with IgG being most frequently affected (0–226 mg/dl) [Kaikov et al., 1991]. Less frequently, IgA and IgM may be depressed or even undetectable [Hitzig et al., 1974]. Failure to produce specific antibody to diphtheria or polio may also occur. B and T cell numbers, DTH test, and response to PHA and alloantigen were normal. Microbicidal activity of neutrophils may also be deficient [Seger et al., 1980]. Clinical manifestations and immunologic abnormalities resolve after cobalamin supplementation.

***Folic acid malabsorption (MIM 229050).*** Deficiency in intestinal folic acid absorption leads to megaloblastic anemia, ataxia, mental retardation, and seizures. Recurrent infections in an affected boy have been described [Urbach et al., 1987]. Humoral defects included undetectable IgA levels and decreased response to PWM. T cell number and response to PHA were decreased. NBT reduction was normal.

***Glycogen storage disease Ib (MIM 232220).*** Patients with a defect in the microsomal translocase for glucose-6-phosphate may present with hepatomegaly, neutropenia, and recurrent infection. Neutrophils show decreased motility, and NBT dye reduction, chemotaxis, phagocytosis, and respiratory burst are variably depressed [Gitzelmann and Bosshard, 1993]. In contrast, monocytes have decreased respiratory burst but usually have normal motility [Ueno et al., 1986]. T cell, B cell, and NK functions are normal.

***Galactosemia (MIM 230400).*** This metabolic defect usually results from a defect in galactose-1-phosphate uridyl transferase and presents with jaundice, hepatomegaly, cataracts, and feeding difficulties. These patients are at increased risk for fatal sepsis from *E. coli* in the neonatal period. Granulocyte chemotaxis is impaired, while bactericidal activity is usually normal [Kobayashi et al., 1980]. Galactosemia may also be rarely due to deficiency of galactokinase. One affected individual suffered from recurrent bacterial infections and had C2 deficiency and decreased neutrophil chemotaxis and bactericidal activity [Borzy et al., 1984].

***Glutathione synthetase deficiency (MIM 266130).*** Glutathione eliminates hydrogen peroxide and protects the cell from oxidative damage. Glutathione synthetase deficiency leads to damage of cellular membranes and microtubules, resulting in impaired phagocytic function [Spielberg et al., 1979]. One affected patient presented with acidosis, hemolytic anemia, and neutropenia during infections. His neutrophils contained only 10–20% of normal glutathione content. After ingestion, excess hydrogen peroxide accumulated (1.6 times normal), and bacterial killing was reduced to 20–25% of control. The cells showed normal phagocytosis, reduction of NBT dye, and chemotaxis. Electron microscopy showed that the patient's neutrophils failed to assemble microtubules during phagocytosis and damage to membranous structures occurred. Vitamin E supplementation led to normalization of microtubule assembly and immunologic function [Boxer et al., 1979].

***Orotic aciduria (MIM 258900).*** This error of pyrimidine metabolism is manifested by retarded growth and development and megaloblastic anemia unresponsive to vitamin B12 and folic acid. Associated anomalies include musculoskeletal abnormalities, strabismus, and congenital heart disease. Affected patients may have lymphopenia and increased susceptibility to infection, including fatal varicella and meningitis. CD4, CD8, and total T cell numbers were decreased in two sibs [Girot et al., 1983]. T cell-mediated killing was reduced to 16% of control level. Proliferation in response to PHA and allogeneic cells was normal. B cell percentage and immunoglobulin levels were normal. Another patient had decreased IgG (251 mg/dl) and undetectable IgA [Alvarado et al., 1988]. Lymphoproliferative response to PHA was normal, but responses to ConA and PWM were 50% of normal. The IgG level normalized after uridine treatment, but the IgA deficiency persisted. Other affected patients have normal immune function [Becroft et al., 1984].

***Methylmalonic acidemia (MIM 251000).*** Metabolic acidosis, lethargy, failure to thrive, and recurrent vomiting are frequent manifestations. Leukopenia occurs in 60% of patients [Matsui et al., 1983]. Various immune abnormalities have been reported. Decreases in B cell or T cell number or IgG level may occur [Church et al., 1984]. Depressed neutrophil and monocyte chemotactic responses have also been noted [Church et al., 1984]. The abnormal findings appear to be independent of serum methylmalonic acid concentrations. Chronic exposure to methylmalonic acid might have led to the observed immune derangements, and subsequent changes in the methylmalonic acid level may not have led to immediate correction of the

immune deficits. Another group found that severe infections were a frequent manifestation and reported three unrelated patients with recurrent infections, all of whom eventually died of infectious causes [Wong et al., 1992]. In the patient examined, B cells were not detected in peripheral blood and were markedly reduced in spleen and lymph nodes. Serum IgG, IgA, and IgM were in the low normal range. CD4 number was decreased. Methylmalonic acid inhibits bone marrow stem cell growth in vitro [Inoue et al., 1981].

***Propionic acidemia (MIM 232000).*** This metabolic defect is associated with acidosis and hyperammonemia, and can lead to mental retardation and death if untreated. Immunologic abnormalities have been occasionally reported [Raby et al., 1994]. Hypogammaglobulinemia and B cell lymphopenia were present during the period of metabolic acidosis. Both defects corrected after the patient's metabolic status improved. T cell number and responses to mitogens were normal, as were proliferative responses to PHA, ConA, and PWM.

***Alpha-mannosidosis (MIM 248500).*** The lysosomal storage disease is characterized by psychomotor retardation, Hurler-like changes, dysostosis multiplex, hepatosplenomegaly, and recurrent infections. The metabolic defect lies in deficiency of alpha-mannosidase which leads to the accumulation of mannose-rich oligosaccharides in neural and visceral tissues. Most patients have recurrent infections. Decreased IgG is the most common immune defect [Desnick et al., 1976]. Defective chemotaxis has been reported, while random migration was intact [Desnick et al., 1976]. Phagocytosis and bacterial killing were slow compared to control neutrophils. NBT dye reduction was normal. Proliferation in response to PHA may be only 20% of normal. Accumulation of mannose-rich molecules may interfere with leukocyte plasma membrane-mediated processes which could result in recurrent infections.

## CHROMOSOME ABNORMALITIES ASSOCIATED WITH IMMUNODEFICIENCY

### Syndromes With Chromosome Fragility and/or Defective DNA Repair

Several syndromes are associated with chromosome instability (Table VIII). Spontaneous and induced chromosome breakage is increased, and defective DNA repair may play a role.

***Bloom syndrome (MIM 210900).*** Affected patients typically have low birth weight, proportionate short stature, skin rashes due to hypersensitivity to sunlight, malar hypoplasia, and telangiectatic erythema of the face. They also show an increased incidence of nonspecific chromosome breaks and immune defects. Decreased IgM is the most common finding [Kondo et al., 1992]. IgG and IgA levels may also be low, but these may normalize over time [Kondo et al., 1992]. Similarly, in vitro PWM-induced immunoglobulin production for all classes may be initially low, but only the IgM synthesis remains persistently low. Interestingly, the number of surface IgM-bearing cells is not reduced, whereas the number of IgM-secreting cells is reduced, implying that the IgM deficiency may be at the level of B cell maturation. T and B cell numbers are normal. Allogeneic response may be decreased [Hutteroth et al., 1975]. PHA response and isohemagglutinin titers are normal. NK cell defects have also been described [Ueno et al., 1985]. This autosomal recessive gene has been mapped to 15q26.1 [German et al., 1994].

***DNA ligase I defect (MIM 126391).*** Webster et al. [1992] described a girl with growth retardation, sun sensitivity, and recurrent ear and lung infections. IgA, IgG2, and IgG3 were decreased, and isohemagglutinins were not detectable. This pattern of immunodeficiency somewhat resembles that seen in Bloom syndrome and ataxia-telangiectasia. At age 17 years, the patient became lymphopenic (800 cells/mm$^3$) with decreased T cells (30%) and no response to PHA. The patient died at

TABLE VIII. Syndromes Associated With Chromosomal Abnormalities: Chromosomal Fragility and/or Defective DNA Repair*

| Name | Inheritance | Associated manifestations | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Bloom syndrome | AR | Short stature, telangiectatic erythema of face, sensitivity to sunlight | T, B, Ph | >130 | 15 |
| 2. DNA ligase I deficiency | ? | Short stature, sensitivity to sunlight | T, B | 1 | 1 |
| 3. Ataxia-telangiectasia | AR | Progressive cerebellar ataxia, telangiectasias (conjunctival), choreoathetosis | T, B | >300 | >180 |
| 4. Fanconi pancytopenia | AR | Radial hypoplasia, hyperpigmentation, pancytopenia | Ph, NK | >700 | >650 |
| 5. Nijmegen breakage syndrome | AR | Microcephaly, mental retardation, prenatal onset short stature, bird-like facies, cafe-au-lait spots | T, B | 14 | 14 |
| 6. ICF syndrome (Immunodeficiency-Centromeric instability-Facial anomalies) | ?AR | Variable immune deficiency, mental retardation, chromosomal instability, facial dysmorphism | T, B, NK | 10 | 10 |
| 7. Xeroderma pigmentosum | AR | Photophobia, conjunctivitis, atrophic and pigmentary skin changes, skin tumors | T, NK | >800 | 35 |

* NK = natural killer cells; see Table I for definitions of abbreviations.

age 19 from pneumonia. Her fibroblasts were killed by unusually low doses of irradiation, and increased sister chromatid exchange was noted. Two miscoding mutations of DNA ligase I were detected. Since cell lines from patients with Bloom syndrome do not show mutations in DNA ligase I, this patient represents a distinct entity. The DNA ligase I locus has been mapped to chromosome 19q13.2–13.3 [Barnes et al., 1992].

***Fanconi pancytopenia (MIM 227650).*** Hyperpigmentation of the skin, cafe au lait spots, and limb defects (especially radial hypoplasia) are typical manifestations. Short stature, abnormal thumbs, microcephaly, genitourinary anomalies, and a characteristic facial appearance (microphthalmia, micrognathia, broad nasal base, and epicanthal folds) are typical. Affected individuals also have an increased incidence of leukemia and show multiple chromosome breaks. Clastogen-induced breakage using diepoxybutane, mitomycin C, or other DNA cross-linking agents is diagnostic of this disorder although the underlying defect is unknown [Auerbach et al., 1989]. Such testing is necessary to distinguish between Fanconi pancytopenia and other syndromes with a similar phenotype. Neutropenia secondary to bone marrow failure occurs in over 95% of patients. NK activity is decreased despite normal NK number, implying an intrinsic cell defect [Froom et al., 1987]. T and B cell functions are generally normal. At least two loci associated with Fanconi pancytopenia have been mapped to 20q [Strathdee and Buchwald, 1992].

***Ataxia-telangiectasia (MIM 208900).*** This condition is marked by progressive cerebellar ataxia, telangiectasias (especially of the conjunctiva), and increased chromosome instability (especially involving chromosomes 7 and 14). Most breaks occur at sites responsible for the assembly of immunoglobulin and the T cell receptor for antigen [Aurias and Dutrillaux, 1986]. An abnormally high number of T cells express an unusual form of the T cell antigen receptor, the gamma/delta receptor [Carbonari et al., 1990]. These findings may indicate that a defect in assembly of these surface molecules may adversely affect differentiation and function of T cells and B cells. More than 50% of patients suffer from recurrent sinopulmonary infections. There are several complementation groups, and the gene for one of these has been localized to 11q22–23 [Gatti et al., 1988], close to the loci for thy-1 and CD3. Multiple immunological defects have been described. Very low or undetectable levels of IgA and IgE are the most frequent aberrations [Fiorilli et al., 1983; Waldmann, 1983]. IgG2 and IgG4 are also often low and an abnormal low molecular weight IgM may be present [Oxelius et al., 1982]. Decreased in vitro antibody production also occurs. Defective antibody response to specific viral and bacterial antigens has been noted. T cell number is often decreased with impaired DTH response and delayed allograft rejection [Waldmann, 1983]. The thymus may be abnormal and have the appearance of an immature or fetal thymus [Waldmann, 1983]. A defect in calcium-dependent signal transduction in T lymphocytes has been reported [Kondo et al., 1993].

***Nijmegen breakage syndrome (NBS; MIM 251260).*** Short stature, microcephaly, bird-like facies, and mental retardation are typical of this syndrome of chromosome instability [Weemaes et al., 1981; Wegner et al., 1988]. The condition is similar to ataxia-telangiectasia in that rearrangements of chromosomes 7 and 14, hypersensitivity to irradiation, and immunodeficiency are present. However, the syndrome is distinct from ataxia-telangiectasia, as the patients do not display either of the cardinal neurocutaneous abnormalities and alpha fetoprotein level is normal. There is an increased risk of lymphoreticular malignancy [Seemanová et al., 1985]. Abnormalities in immunoglobulin levels are variable and include decreases in IgA, IgM, IgG2, IgG4, and/or IgE [Taalman et al., 1989]. Proliferation in response to PHA and PWM is usually decreased. T cell number may be low [Conley et al., 1986].

Some individuals with bird-like facies, short stature, microcephaly, and mental retardation were diagnosed with Seckel syndrome and then subsequently found to have chromosome fragility and hematologic abnormalities [Butler et al., 1987]. These individuals may actually have NBS. Whether NBS represents one end of the spectrum of Seckel syndrome or is a distinct entity is unclear. However, because of the overlap in clinical appearance, NBS should be considered in an individual with features of Seckel syndrome and increased chromosome breakage.

***Xeroderma pigmentosum (MIM 278700).*** Sensitivity to sunlight with development of carcinoma at an early age, freckle-like lesions, photophobia, and poikiloderma (atrophic and pigmentary skin changes) are characteristic of this condition. Some form of immune alteration is found in 4% of patients, while only 1.2% show recurrent infection [Kraemer et al., 1987]. T cell number is decreased, due entirely to decreased CD4 cells [Wysenbeek et al., 1986]. DTH response is decreased, and an inhibitory factor in the patients' serum may cause decreased proliferation in response to PHA [Dupuy and Lafforet, 1974]. NK number is normal, but NK killing is decreased [Norris et al., 1988]. Hypogammaglobulinemia rarely occurs [Kraemer et al., 1987]. Since this condition is heterogeneous, it will be important to determine which types are characteristically associated with immunodeficiency.

***ICF syndrome (MIM 242860).*** This condition is characterized by Immunodeficiency, Centromeric instability (usually chromosomes 1, 9, and 16), and Facial anomalies (hypertelorism, flat nasal bridge, and protrusion of the tongue) [Maraschio et al., 1988]. The chromosomes show an increased frequency of mitotic recombination and formation of multibranched configurations. Mental retardation and severe chronic sinopulmonary, gastrointestinal, and cutaneous infections also occur. The immune defect is variable. Low T cell number occurs [Fasth et al., 1990]. Decreased IgA is the most common defect, while low IgG and IgM are also usually present [Maraschio et al., 1988]. NK cell activity is low, and NK cells were not detectable in one patient [Fasth et al., 1990].

## Chromosome Abnormalities of Number or Structure Associated With Immunodeficiency

Several syndromes with known chromosome abnormalities are associated with immunodeficiency (Table IX).

TABLE IX. Syndromes Associated With Chromosomal Abnormalities: Chromosomal Abnormalities of Number or Structure*

| Name | Inheritance | Associated manifestations | Immune defect | No. of cases | No. with ID |
|---|---|---|---|---|---|
| 1. Trisomy 21 (Down syndrome) | — | Hypotonia, flat facies, slanted palpebral fissures | T, B | >1,000 | >100 |
| 2. Deletion of short arm of chromosome 18 | — | Mental and growth deficiency, microcephaly, ptosis | B | >120 | 2 |
| 3. Deletion of long arm of chromosome 18 | — | Midface hypoplasia, microcephaly, mental retardation, nystagmus | B | >80 | 5 |
| 4. Deletion of chromosome 22:q11 (DiGeorge/velo-cardio-facial syndrome) | — | Aortic arch anomalies, hypocalcemia, facial defects thymic hypoplasia. May be associated with teratogenic exposure | T | >100 | >100 |
| 5. Missing or abnormal X chromosome (XO, isoX, ring X; Ullrich-Turner syndrome) | — | Short stature, webbed neck, amenorrhea | T, B | >1,000 | >20 |

* See Table I for definitions of abbreviations.

The chromosome or chromosome segment involved most likely contains genes important for immune cell development and function, but the identity of the crucial genes is unknown for the entities described.

***Trisomy 21 (MIM 190685).*** Individuals with Down syndrome can experience significant morbidity and mortality due to infections, especially respiratory infections [Ugazio et al., 1990]. Increased IgG and decreased IgM levels occur during late childhood and adolescence [Burgio et al., 1983]. Specific antibody response is low in some patients [Ugazio et al., 1990]. The thymus is often small with a distinct histologic pattern. Proliferation in response to PHA and alloantigens may be reduced. Low IL-2 production and impaired DTH response have also been described [Ugazio et al., 1990]. NK cell number may be increased, but activity is low [Montagna et al., 1988]. Phagocyte number is normal, but chemotaxis and oxidative metabolism, and hence killing, is impaired [Ugazio et al., 1990].

***Chromosome 18 deletions.*** Deletion of the short arm of chromosome 18 (18p−) is marked by mental retardation, growth deficiency, and ptosis, while deletion of the long arm of chromosome 18 (18q−) is characterized by midface hypoplasia, conductive hearing loss, and mental retardation. Decreased or absent IgA has been found in 2 of 6 patients with ring 18, 5 of 15 with 18q−, and 2 of 5 with 18p− [Stewart et al., 1970; Wertelecki and Gerald, 1971]. Thus, decreased IgA levels are found in some, but not all, individuals affected with structural chromosome 18 derangements.

***Ullrich-Turner syndrome.*** Patients with a missing or structurally abnormal X chromosome have short stature, shield chest, congenital lymphedema, and ovarian dysgenesis. The syndrome is associated with an increased risk for upper respiratory and ear infections and autoimmunity. In a review of 29 patients, decreased IgG was found in 48%, decreased IgM in 41%, and decreased IgA in 10% [Lorini et al., 1983]. T and B cell number and PHA and ConA responses were normal in this study. Decreased T cell number, with poor response to PHA and absent DTH, has also been reported [Donti et al., 1989].

***DiGeorge sequence (MIM 188400).*** This condition is a malformation sequence due to defective development of the third and fourth pharyngeal pouches, leading to thymic absence of hypoplasia, conotruncal cardiac defects, and absence or hypoplasia of the parathyroids (leading to hypocalcemia). Typical facies include hypoplastic mandible, short philtrum, ocular hypertelorism, short bulbous nose, and low-set, malformed, or posteriorly angulated ears. Although the causes may be diverse, the underlying pathogenesis of DiGeorge sequence is abnormal migration of cephalic neural crest cells [Bockman and Kirby, 1984], leading to a polytopic developmental field defect [Lammer and Opitz, 1986]. Microdeletions of chromosome 22q11 are found in many cases of DiGeorge sequence [Driscoll et al., 1992] and in a closely related condition, the velo-cardio-facial syndrome [Scambler et al., 1992]. Immune dysfunction may be subtle (partial DiGeorge) with variable T cell dysfunction and normal B cell function and number. In the severe form (complete DiGeorge), T cells may be depleted, and immune function is usually greatly impaired. Serum immunoglobulin levels and specific antibody response are usually low. Some patients may present with normal immune function, and spontaneous remission of clinically significant immune defects often occurs. Decreased PHA response with low CD4 count may be the most accurate predictor of persistent immunodeficiency [Bastian et al., 1989].

The DiGeorge sequence is occasionally found in other malformation syndromes, such as the CHARGE association [Pagon et al., 1981; Siebert et al., 1985]. Thymic hypoplasia or aplasia has also been associated with in utero exposure to several teratogens, including vitamin A [Lammer et al., 1985], ethanol [Ammann et al., 1982], and in infants of diabetic mothers [Gossage et al., 1982; Black et al., 1975]. Thus, DiGeorge malformation sequence can occur as part of several syndromes which disturb cephalic neural crest cell migration during the sixth week of embryogenesis.

## DISCUSSION

In this paper, we have delineated the wide variety of genetic syndromes associated with immunodeficiency. Adding to the recognized primary immunodeficiencies, we describe 64 syndromes in which immunodeficiency has been described in single (10), multiple (26), or most

(28) cases. The defects observed usually involve the T cell (8), B cell (17), or combined (30) defects (Table X). Conditions associated with predominantly phagocytic abnormalities are less common. Natural killer cell abnormalities are also observed. In addition to immunological derangements, these conditions present with characteristic combinations of other physical or metabolic features. Immunodeficiency can occur in association with known metabolic entities, chromosome anomalies, or defined monogenic syndromes. However, the specific mechanisms by which the abnormality affects immune function are generally not known. Similarly, immune defects can occur in the setting of dermatologic, gastrointestinal, or neurologic abnormalities, although the relationship between the immune and extraimmune manifestations is obscure in most cases. Nonspecific causes for frequent infections include malnutrition from gastrointestinal syndromes or loss of skin integrity in the dermatological syndromes. Anatomic abnormalities or impaired neurologic function can lead to poor control of swallowing and resultant aspiration and infection. However, the conditions described here have specific immune defects affecting specific cell types.

The relationship between skeletal growth abnormality and immunodeficiency remains unclear. Abnormalities affecting bone development could conceivably have an effect on the stroma of the bone marrow and hence affect immune cell differentiation adversely. Or, genes critical in the differentiation or growth of immune cells could also play a role in bone development. The cytokines interleukin 1, tumor necrosis factor, and interleukin 6 all affect both immune cells and osteoclasts. Indeed, one well-known primary immunodeficiency, the hyper-IgE syndrome, is associated with osteoporosis and frequent infections. Genes important in skeletal development may be closely linked to genes vital for immune function, and a contiguous gene deletion could affect both systems.

Similar mechanisms might be invoked to explain the relationship between immunologic and neurologic abnormalities. Certain surface molecules such as thy-1 appear on both neuronal cells and T cells. Soluble factors such as interleukin-1 and adrenocorticotropic hormone (ACTH) have been shown to have effects on both T cells and neurons. Thus, molecules important to the function of both the immune and neurologic cells exist, and disruption of the normal production of such molecules could affect both systems.

Several of the conditions described have thymic hypoplasia or aplasia. Thymic hypoplasia is thought to be a result of defective cephalic neural crest cell migration. The causes are many, and thymic/parathyroid hypoplasia is best conceptualized as a developmental field defect in which the various anomalies can be traced to disturbance of cephalic neural crest cells.

Chromosome fragility may affect the proliferation of immune cells or disrupt genes critical for immune development. The breaks could cause disruptions in either the structural or regulatory segments of affected genes. Potential mechanisms include loss of control of expression by deletion of regulatory elements (e.g., pro-

TABLE X. Genetic Syndromes With Constant or Inconstant Immunologic Abnormalities

| |
|---|
| Syndromes associated with T cell immunodeficiency |
| Cartilage-hair hypoplasia |
| Schimke immunosseous dysplasia |
| Papillon-Lefevre syndrome |
| Rubinstein-Taybi syndrome |
| Purine nucleoside phosphorylase deficiency[a] |
| Orotic aciduria |
| Xeroderma pigmentosum |
| DiGeorge sequence[a] |
| Syndromes associated with B cell immunodeficiency |
| Short limb skeletal dysplasia, type 3 |
| Shwachman syndrome |
| Braegger syndrome |
| Fleisher syndrome |
| Toriello syndrome |
| Mulibrey nanism |
| Sclerosing cholangitis with immunodeficiency |
| Enteropathy with villous edema |
| Netherton syndrome |
| Ritscher-Schinzel syndrome |
| Lichtenstein syndrome |
| Hallermann-Streiff syndrome |
| 5′-nucleotidase elevation |
| Transcobalamin II deficiency |
| Propionic acidemia |
| Deletion of short arm of chromosome 18 |
| Deletion of long arm of chromosome 18 |
| Syndromes associated with combined immunodeficiency |
| Short limb skeletal dysplasia, type 1 |
| Shokeir syndrome |
| Mulvihill-Smith syndrome |
| Familial intestinal polyatresia |
| Powell syndrome |
| Primary intestinal lymphangiectasia |
| Dyskeratosis congenita |
| Griscelli syndrome |
| Acrodermatitis enteropathica |
| Wiskott-Aldrich syndrome[a] |
| Omenn syndrome |
| Jung syndrome |
| Vici syndrome |
| Krawinkel syndrome |
| Frenkel-Russe syndrome |
| Good syndrome |
| Schwartz-Jampel syndrome |
| Hutchinson-Gilford syndrome |
| Adenosine deaminase deficiency[a] |
| Multiple carboxylase deficiency |
| Folic acid malabsorption |
| Alpha-mannosidosis |
| Methylmalonic aciduria |
| Bloom syndrome |
| DNA ligase I deficiency |
| Ataxia-telangiectasia[a] |
| Nijmegen breakage syndrome |
| ICF syndrome |
| Trisomy 21 |
| Ullrich-Turner syndrome |
| Syndromes associated with phagocyte immunodeficiency |
| Cartilage-hair hypoplasia |
| Shwachman syndrome |
| Shokeir syndrome |
| Toriello syndrome |
| Enteropathy with villous edema |
| Dyskeratosis congenita |
| Chediak-Higashi syndrome |
| Griscelli syndrome |
| Kotzot syndrome |
| Acrodermatitis enteropathica |

(*continued*)

TABLE X. Genetic Syndromes With Constant or Inconstant Immunologic Abnormalities (*continued*)

| |
|---|
| Omenn syndrome |
| Papillon-Lefevre syndrome |
| Jung syndrome |
| Krawinkel syndrome |
| Rubinstein-Taybi syndrome |
| Dubowitz syndrome |
| Smith-Lemli-Opitz syndrome |
| Seckel syndrome |
| Transcobalamin II deficiency |
| Glycogen storage disease Ib |
| Alpha-mannosidosis |
| Galactosemia |
| Glutathione synthetase deficiency |
| Methylmalonic aciduria |
| Bloom syndrome |
| Fanconi pancytopenia |
| Syndromes associated with NK cell immunodeficiency |
| Chediak-Higashi syndrome |
| Bloom syndrome |
| Fanconi pancytopenia |
| ICF syndrome |
| Xeroderma pigmentosum |

[a]Classified as a primary immunodeficiency by WHO [Rosen et al., 1995].

moters, enhancers) or placement of a structural gene, through a translocation, under the control of a different set of regulatory elements. Both of these could result in disruption of control of expression of the gene, leading to over- or under-production of the gene product. The chromosome breakage syndromes show evidence of both immunodeficiency and increased risk for malignancy. The risk for malignancy can be due to loss of normal control of expression over genes important for cell growth regulation. Alternatively, the link between immunodeficiency and malignancy may be more direct in that failure to maintain normal immune status may lead to decreased surveillance and reduced clearance of tumor cells. In this situation, the chromosome breaks would disrupt genes important for the normal differentiation and production of immune cells, and malignancy would be more likely to occur.

The occurrence of immunodeficiency with other physical abnormalities could result from several underlying pathogenetic mechanisms. First, a mutation in a polypeptide common for the function, regulation, or development of both the involved systems could occur. This could have a direct effect on the structure, enzymatic activity, or regulation of the affected gene. A second possibility is that distinct genes that are critical in the development of one of the involved systems could be closely linked to a gene that is important for the immune system. A contiguous gene deletion would affect both groups. Third, insults at crucial times in embryological development could affect more than one organ system if both were developing at that time. Fourth, a derangement in one system (e.g., bone or thymus) could impair proper development of immune cells by providing an inhospitable environment. Impairment in function of stromal elements could disturb support of normal immune development. Alternatively, long-term exposure to acidosis or toxic metabolites, as may be found in some inborn errors of metabolism, could also affect function of the immune system.

It is hoped that this delineation of immunodeficiencies that occur with recognizable syndromes will be useful both for basic science investigators and clinical practitioners. A clinician faced with a child who manifests clinical immunodeficiency and other unusual traits might gain useful information regarding prognosis and treatment, if the diagnosis of a previously described syndrome could be made. Also, the recognition that a patient presenting with a particular syndrome is at increased risk for immune deficiency would be important in management of the patient. Finally, if the mode of transmission for a given rare immunodeficiency syndrome is known, it may provide useful information for genetic counselling.

The conditions described herein could also be fruitful areas for future research. Unusual or infrequent co-occurrences of seemingly unrelated abnormalities might imply that some common process is involved and thereby help to suggest potential candidate genes. As the critical elements in the pathogenesis of defined genetic syndromes or immunodeficiency states is better understood, these cases could be useful in clarifying the relationship between the immune system and developing organ systems.

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